

Advancements in Oncology – The use of Nanotechnology in the
detection and diagnosis of cancers

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ABSTRACT

Nanotechnology refers to the development and engineering of manipulating matter at the molecular scale to create devices with novel chemical, physical and biological properties. This emerging field involves scientists from many different disciplines, including physicists, chemists, material scientists and biologists. Nanotechnology is being applied to almost every field imaginable, including magnetics, optics, biology and now medicine.

Nanotechnology is undoubtedly the revolutionising technology of the future with immense potential to radically alter traditional methods of diagnosing and treating cancerous cells. Pioneering research continues at the National Cancer Institute where they believe that nanotechnology can provide rapid and sensitive detection of cancer-related molecules, enabling scientists to detect molecular changes in the genetic code in even a small percentage of cells. This paper aims to discuss the basic principles proposed in the use of nanotechnology in medicine mainly addressing its use in the diagnosis and treatment of cancers.

INTRODUCTION

The history of Nanotechnology:

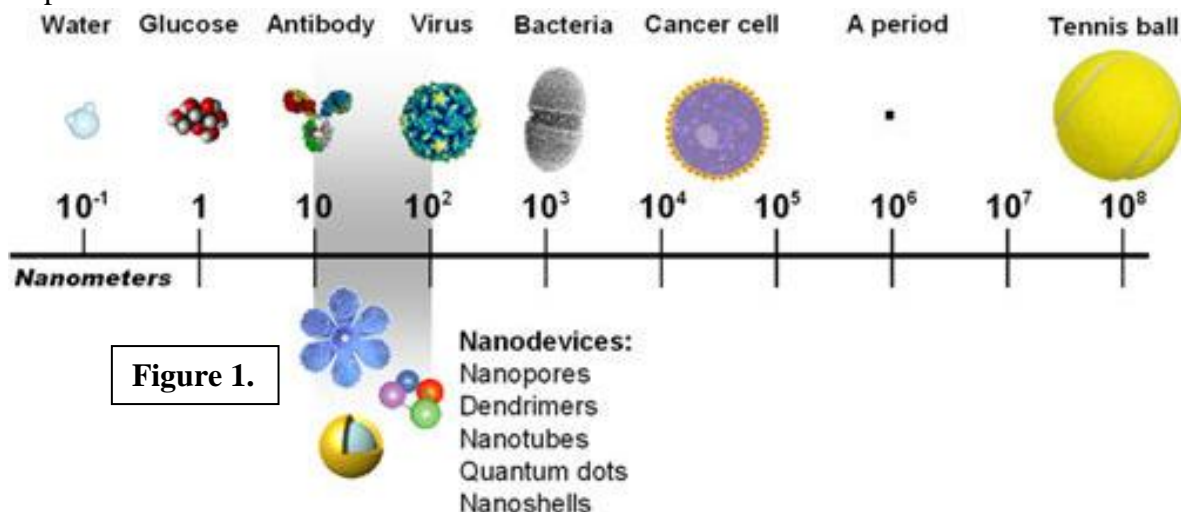
On the 29th December 1959, Richard Feynman gave a completely theoretical and seemingly brilliant speech titled “There's Plenty of Room at the Bottom” where he described how the laws of physics do not limit our ability to manipulate single atoms and molecules beyond miniaturization.

Feynman described such atomic scale fabrication as a “bottom-up” approach to manufacturing that would provide components made of single molecules, held together by covalent forces that are far stronger than the forces between macro-scale components. Examples that illustrate this concept of natural assembly include viruses; a similar size to nanodevices, which self-construct once they have finished manufacturing component proteins in the host cell.

Sizing things up:

Nanoscale devices are one hundred to ten thousand times smaller than human cells and similar in size to large biological molecules such as enzymes and receptors. As an example, haemoglobin is approximately 5 nanometres in diameter. Nanoscale devices smaller than 20 nanometres can move out of blood vessels and they circulate through the body and can readily interact with biomolecules on both the surface and inside cells. This miniscule size subsequently gives nanoparticles the potential to detect disease and deliver treatment in ways unimagined before now. However, this same feature poses several concerning risks as discussed in the following pages.

Figure 1 below illustrates the comparatives in size between nanodevices and their biological companions.



At the nanoscale, fundamental chemical, biological and optical properties differ significantly from properties of micrometer-sized particles or bulk materials, and this is because of their surface area.

When mentioning nanodevices, surface area is significant because nanoparticles have a considerably greater surface area than other bulk material of the same mass.

As an example, the surface area of a solid material is 6cm^2 , comparably, the surface area a nanoparticle is 6,000 square metres; $\frac{1}{3}$ larger than a football field.

Therefore the collection of nano-sized particles with their enormous surface area will be exceptionally reactive because more than a third of their chemical bonds are on the particles' surface.

Figure 2, right, illustrates above; the smaller the particle, the greater its surface area is.

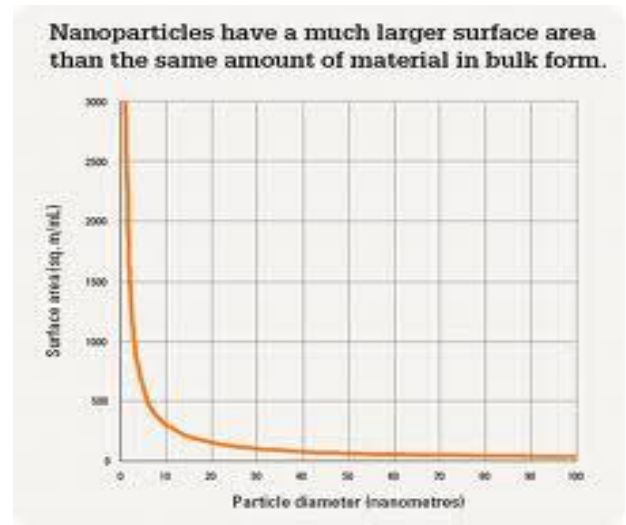


Figure 2.

Shape matters:

Carbon with the identical chemical composition is found in multiple structural forms, called allotropes, which have significantly different properties. For example, in crystalline form, pure carbon is found as graphite (very soft), diamond (very hard), and various sizes of Buckminsterfullerenes; because the pattern of molecular bonds differ depending on the number of carbon atoms.

Until 1985, it was believed that pure carbon came in only two crystalline forms: graphite (whose hexagonal crystal lattice lies in a two-dimensional plane) and diamond (whose cubic crystal lattice extends in all three dimensions). That year, hollow cages of 60 carbon atoms shaped like footballs were first made in the laboratory - a new stable crystalline form of carbon so significant it was recognized by the Nobel Prize in Chemistry in 1996. The hollow cage was named after the architect Richard Buckminster Fuller; a buckyball or fullerene. Since then, stable fullerenes of 70, 74, and 82 carbon atoms have also been synthesized. (See Figure 3, below)



Figure 3. Structures of Diamond, Graphite and Buckminsterfullerene

Current consumer products involving nanotechnology:

The revolution of the “nano trend” seems limitless and these advancements mean various specialties in medicine are currently able to benefit.

Nanotechnology has successfully enabled scientists to create anti-microbial bandages; these wound dressings contain silver nanoparticles that act as a bactericide. It has been proven to be effective as bactericidal agents due to their large surface area and high reactivity. A larger surface area means more silver can interact with body fluids to encounter and inhibit microbes.

Meanwhile, hundreds of thousands of sufferers of type 1 diabetes worldwide can now benefit from Nanotechnology. This condition affects the body’s defence mechanisms, where pancreatic beta cells that produce insulin are destroyed; subsequently fluctuating blood sugar levels. New methods of monitoring blood sugar levels have been developed with the use of fluorescent Nanotubes. Carbon Nanotubes are useful in measuring the concentration of glucose in the blood and works by exposing the electrons in the Nanotubes to near-infrared light and the intensity of the fluorescence is using a spectrometer, and continuous readings are given to the patient.

Moreover, instead of only measuring blood glucose levels, research at the University of Texas has led to a device being produced that controls levels of glucose by mimicking the pancreas without the need for continual monitoring and injecting of insulin. Concanavalin A, a blood sugar sensing protein releases insulin -coated liposomes that bind to the blood sugars and insulin is released into the bloodstream where it is transported to other parts of the body.

Scientists are in the developing stages of producing nanofilters comprised of nano-sized argonide particles. The disposable filter is able to retain out 99.9999+% of viruses and bacteria; sterilizing drinking water. Third World peoples will benefit the most, providing resolutions to the issue they face, where contaminated water leads to thousands of deaths each day.

One of the most exciting proposals is the use of nanotechnology in tissue repair and regenerative medicine. Currently, doctors can only encourage tissues to repair themselves through drugs and surgery. The focus of regenerative medicine is to work with the body’s own repair mechanisms, to prevent, and treat disabling chronic diseases such as diabetes, osteoarthritis and degenerative disorders of the cardiovascular and central nervous system. Nanotechnology aims to establish a cellular basis for the development of innovative disease modifying therapies.

I will now look to explore possible uses of nanotechnology in cancer diagnosis and treatment based on the concepts outlined.

DISCUSSION

A cancer or malignant neoplasm is the malignant growth or tumour caused by abnormal and uncontrolled cell division, intrusion on and destruction of adjacent tissues. Tumours can be either benign or malignant, and although benign tumours are not considered life-threatening, malignant tumours can metastasize, where the group of diseased cells spread to other locations in the through the lymphatic system or the blood stream.

P53 is a tumour suppressor gene that is activated in response to DNA damage and other cellular stresses. It is responsible for activating transcription of CKIs (cyclin kinase inhibitors), which stop the cell cycle. If p53 is mutated or not functional, the cell cycle cannot stop, and damaged cells will continue to proliferate thus leading eventually to cancer. 80% of all human tumours contain a mutation or deletion of the P53 gene. Figure 4 (right) illustrates the steps for cells to become cancerous.

Cancer is the most common cause of death with more than 10 million people diagnosed every year and 30% of these result in death. However, recent research shows that mortality rates for cancer are decreasing due to early diagnosis and more effective treatment. However, more people are being diagnosed per annum, meaning that there is an urgent need for better methods of treatment and diagnosis in the future.

Although there is no thorough cure for cancer at later stages, early stage cancer is generally treatable and the prognosis is promising and this would subsequently improve the cure rate

Current diagnosis methods:

Current imaging methods can only readily detect cancers once they have made a visible change to a tissue, by which time thousands of cells will have proliferated and perhaps metastasized. And even when visible, the nature of the tumour—malignant or benign—and the characteristics that might make it responsive to a particular treatment must be assessed through biopsies.

A biopsy is the removal of a lesion and the tissues from the histological examination is then sent to a lab to be confirmed by a pathologist.

Techniques used for Incisional and Excisional biopsies include Punch, Shave, and Needle biopsies. The technique used depends on the goal of the biopsy, the cancer type and the location of the cancer.

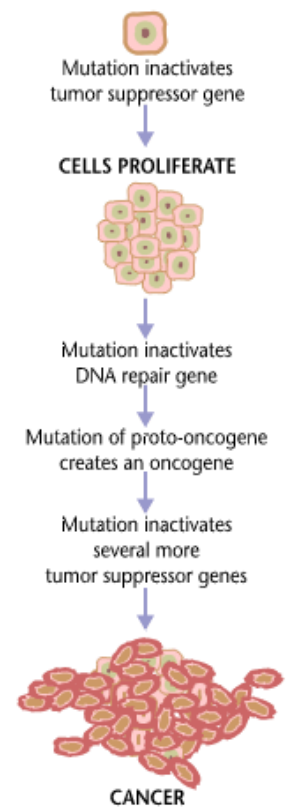
Secondly, non-invasive in vivo imaging techniques that use the reflection of sound waves and radio waves to produce images in Ultrasound, MRI scans and CT scans.

Implications concerning current therapies:

Currently, current treatments such as chemotherapy and radiotherapy are the most effective treatment available for cancer. However, their lack of accuracy and ability to specify between cancerous and healthy B cells diminishes its effectiveness and so its inability to target cancerous cells results in the damaging of neighbouring healthy cells.

One of the biggest concerns regarding chemotherapy is that if patients fail such a treatment, they only have a mere 10% chance of being successfully treated by alternative therapies such as immunotherapy, hormone therapy or radiotherapy.

Figure 4.



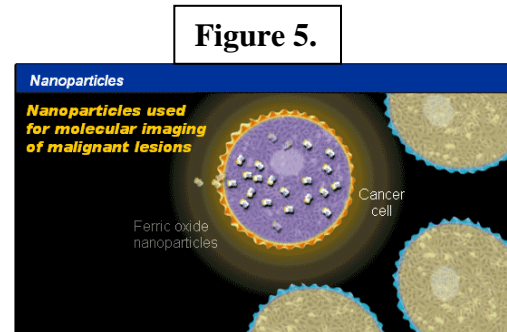
The future of cancer diagnosis and therapy:

Nanoscale devices have the potential to radically change cancer diagnosis and treatment for the better and to dramatically increase the number of highly effective therapeutic agents. Most animal cells are 10,000 to 20,000 nanometres in diameter. This means that nanoscale devices (less than 100 nanometres) can enter cells and interact with DNA and proteins.

Subsequently, these sensitive tools developed may be able to detect disease in very small samples of cells or tissue. Below I will discuss the various nanodevices and their benefits.

Nanoparticles:

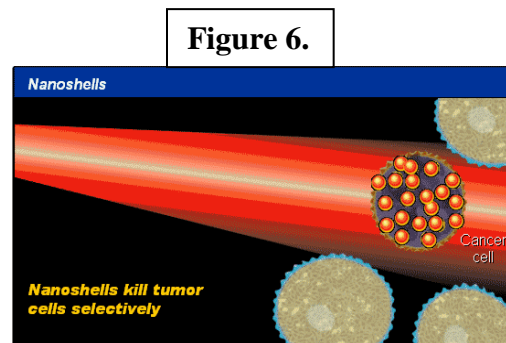
Nanoparticles have spherical structure and are mostly hollow, providing a central reservoir that can be adorned with anticancer drugs, detection agents, imaging agents or reporters, which signal if a drug is having a therapeutic effect on the patient. Most nanoparticles are constructed to be small enough to pass through blood capillaries and enter cells. Figure 5 shows Ferric oxide nanoparticles entering a cancerous cell and subsequently making the lesion visible.



These nanoparticles give us the ability to see cells and molecules that otherwise cannot be detected through conventional imaging. The ability to pick up what happens in the cell - to monitor therapeutic intervention and to see when a cancer cell is mortally wounded or is actually activated - is critical to the successful diagnosis and treatment of the disease.

Nanoshells:

They are a type of nanoparticle that has a core of silica and a semiconducting metallic outer shell. These nanoshells are then injected safely in cancer lesion sites. These Nanoshells are coated in gold that can locate a cluster of cancer cells and attach to them; acting as "biomarkers". Once they reach a target cancer cell, they can be irradiated with near-infrared light or supplied mechanical, radio frequency or optical external energy that will create an intense heat, making the gold reactive under such temperatures that selectively kills the tumour cells.



The result is greater efficacy of the therapeutic treatment and a significantly reduced set of side effects.

Each nanoshells is only 100 nanometres in diameter and so are small enough to travel through the bloodstream, which allows successful treatment regardless of the situation of the problem, therefore allowing treatment of tumours that could otherwise have been fatal as they were inaccessible for surgery. Researchers at Rice University, under Prof. Jennifer West's supervision were able to demonstrate the use of 120 nm diameter nanoshells to kill cancer tumours in mice. Those nanoshells can be targeted to bond to cancerous cells by conjugating antibodies or peptides to the nanoshells surface. Figure 6 shows a gold-coated nanoshells occupying a cancer cell and being irradiated by near-infrared light; killing the cell.

Nanopores:

Another intriguing nanodevice is the Nanopore. These tiny holes that allow deoxyribonucleic acid (DNA) to pass through one strand at a time are believed to make DNA sequencing more efficient and thus immensely improving diagnostic techniques for cancer.

Improved methods of reading the genetic code will help researchers detect mutations in the base sequence that may contribute to cancer. Mutations in genes create a non-functioning enzyme. As DNA passes through a Nanopore, scientists can monitor the shape and electrical properties of each base; Guanine, Tyrosine Adenine and Cytosine, on the strand. These bases are usually complementary and make up the primary structure of a protein. Scientists can use the passage of DNA through a Nanopore to decipher the encoded information, including mutations in the genetic code; such as the deletion/substitution/insertion of a protein known to be associated with cancer such as the deletion of P53 (as stated above) that causes 80% of all cancers.

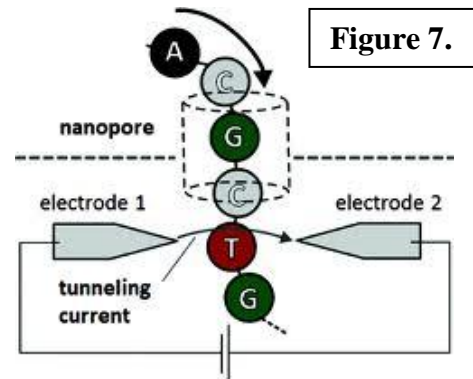


Figure 7.

Figure 7 (right) shows a single strand of DNA passing the Nanopore; identifying T as the incorrect complement to C because its of insertion between C-G.

Quantum dots:

Existing ways of labelling cancer-associated sequences of DNA rely on the light-emitting properties of radioisotopes and contrast. These labelling techniques are limiting in the fact that the radioisotopes have short half-lives and so persist in the body for such a short amount of time that they lose their glow before tracing is complete. There is now a great demand for more reliable labelling in finding cancer signatures present in cells or tissues.

Quantum dots are tiny crystals that glow when they are stimulated by ultraviolet light. To detect cancer, scientists can design quantum dots that bind to sequences of DNA that are associated with the disease. When the quantum dots are stimulated by UV light, they emit their unique labels, making the critical, cancer-associated DNA sequences visible, aiding pathologists to identify the tumours' direct region. More advantages to quantum dots are that they eliminate the need for biopsies, and that they are highly stable against photo-bleaching.

Issues surrounding Nanotechnology – environmental, ethical, and toxicological considerations

Nanotechnology is showing promising advancements in medicine and will undoubtedly strike positive effects in our health and welfare. However, we should be cautious and aware of possible unwanted side-effects.

In general, experts report nanoparticles are more bioactive and toxic due to their size. Their ability to interact with other living systems increases because they can easily cross the skin, lung, and in some cases the blood/brain barriers. Once inside the body, there may be further biochemical reactions like the creation of free radicals that damage cells. Below I have discussed several studies concluding dangers that have arisen due to their most beneficial feature; their size.

Nanoparticles have an extremely large surface area, leading to a greater inflammatory response in the body than the same amount of larger particles. They are also small enough to enter the lining of the lungs, enter the bloodstream and interact with other organs. There is some evidence that nanoparticles can move into the brain along the olfactory nerve, so this is completely circumventing the blood-brain barrier.

Carbon Nanotubes in the lungs are mistaken for biological materials instead of foreign material and are used as a framework for repair, where collagen and other cells accumulate around the tube. Although this may be beneficial in other parts of the body, in the lungs this reduces surface area of the alveoli; meaning that less oxygen can occupy the lungs and so decreasing the rate of diffusion of gases across epithelial cells.

In March 2004 tests conducted by an environmental toxicologist found extensive brain damage to fish exposed to buckminsterfullerenes for a period of just 48 hours at a relatively moderate dose of 0.5 parts per million. From these results, it was concluded that further studies on the accumulation of fullerenes were necessary.

These problems make it difficult to assess the safety of nanotechnology for health related purposes. This is mainly because researchers cannot predict exactly how the body reacts to such foreign material. Each person's immune system could react differently to nanodevices; where one person's Leukocytes would engulf the particle in defence, another person In addition, a person suffering with AIDS will not experience this. Similarly, immunological tolerance may develop against tumour antigens, so the immune system no longer attacks the tumour cells and thereby assists spread of cancer cells

Other nanoparticles have also been shown to have adverse effects on the human body. Research from University of California in 2002 revealed Quantum Dots (cadmium selenide) can cause cadmium poisoning in humans. Furthermore, British scientist Vyvyan Howard published findings that indicated gold nanoparticles are small enough enter through a mother's placenta to the fetus; harming the unborn baby.

From 1997, scientists at Oxford discovered nanoparticles used in sunscreen created free radicals that damaged DNA; potentially causing cancer.

Not enough data exists to know for sure if nanoparticles could have undesirable effects on the environment. In free form, nanoparticles can be released in the air or water during production and accumulate in the soil, water or plant life. It is not currently known how these nanopollutants could be removed from the environment because most traditional filters have pores that are too large to catch nanoparticles.

CONCLUSION

In conclusion, the science of nanotechnology is and will undoubtedly influence medicine in the coming decades, and as explained in this research paper; the techniques in which nanotechnology promotes early diagnoses prevents cancerous cells from multiplying and metastasizing, and socially, family members are mentally prepared for the stages towards a recovery.

As explored in the paper, nanodevices overcome the many biological, biophysical and biomedical barriers that the body intervenes against foreign material, such as the administration of contrast agents, so the patient will not incur negative side effects. On the contrary, Ecotoxicological impacts of nanoparticles and the potential for accumulation in plants and micro-organisms remains under-researched. Currently, nanoparticles are being considered a new class of non-biodegradable pollutant. In my proposal, it is my strong opinion that further studies should be made regarding how to remove nanopollutants from the air. Moreover, nanoparticles will eventually need to be disposed of as waste and the difficult challenge will be how this can be achieved safely. It is evident that this process will be far from straightforward but it is crucial that further research is done to ensure the safety of future consumers.

The revolution of the nanotrend will not be forgotten by researchers and scientists. More research will be conducted to prove the safety and reliability of Nanotechnology and it is definite that we will be seeing more of these devices in our pharmaceutical drugs and day to day products as the benefits of Nanotechnology outweigh the risks, and are fundamentally more effective than the current treatments available in this generation.

“What we are seeing is the beginning of a revolution, caused by our ability to work on the same scale as nature. Nanotechnology will affect every aspect of our lives, from the medicines we use, the power of our computers, the energy supplies we require, the food we eat, the cars we drive, the buildings we live in and the clothes we wear” – Tim Harper, founder of the European Nano Business Association.

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